Journal of Law and the Biosciences, 1–6
doi:10.1093/jlb/lsx021
Peer Commentary

Comment on mitochondrial replacement techniques and the birth of the 'first'

Rebecca Dimond[1,*] and Atina Krajewska[2]

1. School of Social Sciences, Cardiff University, 12 Museum Place, Cardiff CF10 3BG
2. Sheffield Law School, Bartolome House, Winter Street, Sheffield S3 7ND
*Corresponding author. E-mail: DimondR1@cardiff.ac.uk

Palacios-Gonzalez and Medina-Arellano present an insightful account of the world's first birth following the use of mitochondrial replacement techniques (MRT) by a US doctor, Dr Zhang, through his affiliated clinic in Mexico. Their article contributes to understanding the complex local and global landscapes of reproductive technologies, and provides a counterbalance to the widely publicized statement that the US scientists crossed borders to perform the procedure because there are 'no rules' in Mexico. Their article is no doubt timely. With many other countries considering how to negotiate MRTs within their own legal frameworks, the birth of the 'first' baby, alongside the UK decision to explicitly legalize MRTs, could have international implications.[1,2] By focusing on the UK context and our own understanding of Mexican law, this comment provides further explanation of the international significance of the Mexico announcement and the difficulties of responding to the rapid pace of development of genetic technologies.

Palacios-Gonzalez and Medina-Arellano conclude that the scientists have acted illegally, breaching several provisions of the federal and state law. We do not wish to dispute the authors' interpretation of the law. However, we would like to suggest that an alternative view of MRTs could lead to different legal conclusions concerning the lawfulness of the technique in Mexico. The authors claim that the procedure conducted by Dr Zhang violated the General Health Law and its accompanying Regulations on

1 I.G. Cohen & E.Y. Adashi. *Preventing Mitochondrial DNA Diseases: One Step Forward, Two Steps Back*, 316 JAMA, 273–4 (2016).

2 S. Varvaštian. *UK's Legalisation of Mitochondrial Donation in IVF Treatment: A Challenge to the International Community or a Promotion of Life-saving Medical Innovation to be Followed by others*?, 22 Eur. J Health Law 405–25 (2015).

Health Research, because MRT is not an experimental procedure that 'solves sterility problems'. Furthermore, they claim that because it involves human subjects additional sanctions for breaching the law will apply. The first claim, if accepted as correct, raises questions about the process, in which pre-implantation genetic diagnosis (PGD) has become approved in Mexico. After all, PGD, like MRTs (and unlike in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI)) does not in itself treat infertility. Nor is it possible to identify the precise moment, in which it became a fully acceptable clinical procedure. This is because the clear distinction between research and clinical practice stipulated in legal documents remains almost impossible to maintain in practice. This fluidity is exacerbated in the case of novel reproductive technologies, the full consequences of which will not be known for years, or even generations, to come. With regard to the second point, it could be argued, albeit controversially, that MRT consists of several stages—the experimental stage involving modification of oocytes and embryos (not considered persons under Mexican law) and the assisted reproduction procedure itself (involving human subjects), which is a widely accepted medical practice. Of course, this interpretation might seem far-fetched to many. Alas, the UNESCO and UN *soft law* instruments offer limited assistance and do not impose justiciable obligations on Mexico. Therefore, the urgent need for national regulation of reproductive technologies, voiced by the authors, is clear and undisputed. Can the UK example provide guidance in this respect?

In contrast to Mexico, where law concerning human reproduction remains scarce and contested, the UK legal position is unambiguous. The Human Fertilisation and Embryology Act 1990 prohibits germline genetic modification. However, the 2008 amendments opened the possibility for the UK government to legalize MRT, subject to Parliamentary approval. When the latter was obtained in February 2015, the UK became the first country in the world to explicitly legalize MRTs.[3] Whereas US reports about MRT[4] have mainly drawn on expert opinion and deliberation, the UK's approach is based on a model of public engagement and dialog.

The UK has a history of close yet permissive regulation combined with a framework for transparent public debate, and was therefore well placed to embark on the review process which included exploration of the scientific state of the art and calls for evidence to explore public attitudes and ethical implications. The Human Fertilisation and Embryology Authority (HFEA), which regulates the use of gametes and embryos in the UK was responsible for gathering evidence on the safety and efficacy of the techniques, and in the provision of clinical licenses. Four scientific reviews were organized by the HFEA at the request of the Department of Health in 2011, 2013, 2014, and 2016.[5] The reviews raised several questions relating to the novel features of mitochondria and MRT. These included the risks of 'carry over' (where faulty mitochondria could remain attached to the nucleus during transfer) and the nature of the interactions between

---

3 C. Jones & I. Holme. *Relatively (im)material: mtDNA and Genetic Relatedness in Law and Policy*, 9 Life Sci. Soc. Pol'y 1–14 (2013).

4 National Academies of Sciences, Engineering, and Medicine. Mitochondrial replacement techniques: Ethical, social, and policy considerations (2016). doi: 10.17226/21871 (accessed Apr. 24 2017).

5 HFEA. Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 (2016).

mitochondrial DNA and nuclear DNA, recommending mtDNA haplogroup matching 'as a precautionary measure' (p7) when selecting a donor.

One of the most significant aspects of the review was the conclusion that there was no scientific evidence to suggest differences in safety between maternal spindle transfer (MST) and pronuclear transfer (PNT). On this basis, both techniques were legalized, although the UK has continued to prioritize the development of PNT over MST. Palacios-Gonzalez and Medina-Arellano's article and the decision of the Jordanian family to use MST highlight that there are clearly ethical reasons why PNT, which involves creating and destroying an embryo in the process, might attract more objections.

The final UK scientific report published in 2016 agreed with the findings of the previous reports, concluding that the techniques were 'not unsafe'. The ambiguity of this statement highlights the difficulties of legislating for novel reproductive technologies. A 'cautious' approach was recommended, but it was ultimately considered appropriate 'to offer mitochondrial donation techniques as clinical risk reduction treatment for carefully selected patients' (p7). The result is that in the UK only women at risk of having a child with severe mitochondrial disease are legally allowed to access MRTs.

Alongside concerns about safety were discussions about the ethical issues of MRTs. Following their own call for evidence, the Nuffield Council on Bioethics[6] identified several ethical issues as significant, including the potential for harm, the implications for the child's identity, the relationship between child and donor, and because of germ line changes, whether MRT represented a 'slippery slope' towards human enhancement and manipulation of nuclear DNA.[7] Despite differences between countries' regulatory structures, it is possible that such ethical concerns will be shared.[8] The Council concluded that it would be ethical for the techniques to be used by families as long as they were considered safe and effective and families were offered support.

How or whether to monitor the health of the child and future generations was a key concern throughout the mitochondria debates. Many wanted to avoid a repeat of the US situation where it is only now that a project is underway to monitor the health of surviving children born through a similar technique of cytoplasm injection in 2000.[9,10] In the UK, the HFEA requires clinics to explain to the parents about the benefits of follow-up, while noting that consent to follow-up cannot be mandatory.[11] Zhang has now provided further details of the procedure, and appears to be committed to

---

[6] Nuffield Council on Bioethics. Novel techniques for the prevention of mitochondrial DNA disorders: an ethical Review. London: Nuffield Council on Bioethics (2012). http://www.nuffieldbioethics.org/mitochondrial-dna-disorders (accessed July 6, 2017).

[7] Also see A.L. Bredenoord, G. Pennings & G. De Wert. *Ooplasmic and Nuclear Transfer to Prevent Mitochondrial DNA Disorders: Conceptual and Normative Issues*, 14 Human Reprod. Update 669–78 (2008); Dimond R. *Social and Ethical Issues in Mitochondrial Donation*, 115 Brit. Med. Bull. 173–82 (2015).

[8] R.J. Castro. *Mitochondrial Replacement Therapy: the UK and US Regulatory Landscapes*, 3 J Law Biosci. 726-735 (2016).

[9] J. Cohen J & M. Alikani. *The biological basis for defining bi-parental or tri-parental origin of offspring from cytoplasmic and spindle transfer*, 26 Reproductive Biomedicine Online. 535–537 (2013).

[10] J.A. Barritt et al. *Mitochondria in Human Offspring Derived from Ooplasmic Transplantation: Brief Communication*, 16 Human Reprod. 513–6 (2001).

[11] HFEA 2015. Regulating Mitochondrial Donation (September 2015). HFEA (16/9/2015)764.

tracking the health of the child.[12,13] However, the Jordanian family have declined further tests to assess levels of faulty mitochondrial DNA unless there are obvious health benefits. Interestingly, this paper provides confirmation that Zhang has followed a similar protocol to that which has been agreed in the UK, but the family's reluctance to submit for extensive testing highlights the reality of blurring health and illness in the context of assisted reproduction. It also provides a reminder that for the first cohort of any reproductive technology, there will always be a desire to collect evidence about health and efficacy to inform future use, potentially leading to a tension between the wishes of the family and those of the clinic or scientific institution.

As a baby born through MRT will inherit genetic material from three people, one of the main questions throughout the MRT debates was the nature of the relationship between child and donor. Media coverage was often dominated by headlines about 'three parent babies', with the mitochondria donor identified as a 'second mother' or 'third parent'.[14] But alarmist headlines aside, the question about genetic relatedness is of considerable legal importance. Mitochondrial donation posed a challenge to the UK legal framework because it involves the transfer of genetic but not nuclear material, and this led to uncertainty as to how it should be conceptualized. Egg donation and tissue donation are dealt with in very different ways within UK law, particularly around anonymity and access to information. The HFEA[15] has settled the matter in the UK, at least for the time being, deciding that there was no legal obligation between the child and donor. However, the child can have access to non-identifying information such as screening tests, family health, and personal information provided by the donor, with the donor having the right to know whether their donation has produced a child.[16]

Importantly, the UK situation highlights the factors that can facilitate support for MRT and a change in law, and in this brief comment we highlight two aspects. The first example is the Department of Health's use of a particular definition of genetic modification[17]: 'The working definition that we have adopted is that genetic modification involves the germ-line modification of nuclear DNA (in the chromosomes) that can be passed on to future generations. This will be kept under review' (p15). This 'working' definition was closely aligned with approval for MRT because it ruled out MRT from constituting genetic modification. The implication is that legalizing MRT would not need to be disruptive, and it would not lead to the 'slippery slope' associated with

---

[12] J. Zhang et al. *Live Birth Derived from Oocyte Spindle Transfer to Prevent Mitochondrial Disease*, 34 Reprod. BioMed. Online 361–68 (2017).

[13] M. Alikani et al. *First Birth Following Spindle Transfer for Mitochondrial Replacement Therapy: Hope and Trepidation*, 34 Reprod. BioMed. Online 333–36 (2017).

[14] R. Dimond & N.S. Stephens. *Three Persons, Three Genetic Contributors, Three Parents: Mitochondrial Donation, Genetic Parenting and the Immutable Grammar of the 'Three x x'*, Health (2017). doi: https://doi.org/10.1177/1363459316689380 (accessed July 6, 2017).

[15] Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 (SI 2015/572) http://www.legislation.gov.uk/uksi/2015/572/contents/made?page=5 (accessed July 6, 2017).

[16] R. Dimond. *Techniques of Donation: 'Three parents', Anonymity and Disclosure*, 3 J Med. Law Ethics 165–73 (2015).

[17] Department of Health. Mitochondrial Donation: Government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child 22 July 2014. https://www.gov.uk/government/consultations/serious-mitochondrial-disease-new-techniques-to-prevent-transmission (accessed July 6, 2017).

human modification (which is particularly associated with modifying nuclear genes). By supporting this definition, the government were accused of misleading the public, dishonesty, and acting by stealth.[18]

Secondly, the UK debates involved emotional appeals in support of the change in law. Mitochondrial disease was presented as affecting the lives of thousands of women and MRT as having the potential to eliminate mitochondrial disease from families. [19] The debates were dominated by emotive narratives of patient suffering, with parents of critically ill children appearing in news reports and public meetings around the time of the parliamentary debates. Their stories, always in support of MRT, were much more powerful than the arguments presented by those who stood against the change. As a result, MRT became erroneously synonymized as a treatment and cure for children already born with the disease, and opposition needed to be carefully negotiated. This was evident from a House of Commons debate where one MP stated 'I simply do not understand how opponents of this [MRT] can argue that they want to continue to inflict that sort of suffering on so many children'.[20]

The Mexico case provides an opportunity to question national regulatory approaches within the rapidly developing global landscape of genetic intervention. It highlights the importance, but also the practical difficulties, of supporting transnational law, which regulates cross-border flows of human tissue, people, services, and knowledge. Practicing lawyers have been grappling with these issues for years, but the theoretical debates are still underdeveloped.

Dr Zhang was heavily criticized not just for apparently circumventing US law, but also for not following scientific etiquette, particularly in relation to transparency in relation to how he carried out the techniques, announced the birth and published the scientific details. Dr Zhang's recently published account of the process does not refer to the legality of his position and this is where Palacios-Gonzalez and Medina-Arellano have been able to contribute to the debate. They raise a legitimate concern that Zhang's work will lead to conservative restrictions on reproductive science affecting scientific progress in Mexico which would also have a direct effect on Zhang's Mexican clinic. However, the hope is that every conservative turn can also bring a more liberal wave.

MRT is a contemporary technology, which has challenged legal frameworks and prevailing cultural assumptions about the symbolic and biological significance of genetic material. For many, the mitochondria debates and the UK position towards MRT continue to prove that the UK is a 'gold standard' in reproductive regulation. It can be difficult to make comparisons between countries, such as Mexico and the UK, which have very particular legal traditions and where the law operates within an entirely different socio-political and moral context. Mexico has a deeply Catholic, traditional society, where debates about sexuality and reproduction are highly politicized. Within this context, and despite a general agreement that regulation is needed, doctors and

[18] S. Connor, *Exclusive: Scientists Accuse Government of Dishonesty over GM Babies in its Regulation of New IVF Technique*, The Independent, July 28, 2014. http://www.independent.co.uk/news/science/exclusive-scientists-accuse-government-of-dishonesty-over-gm-babies-in-its-regulation-of-new-ivf-9631807.html (accessed July 6, 2017).

[19] G.S. Gorman et al. *Mitochondrial Donation: How Many Women could Benefit?*, 372 N Engl J Med. 885–7 (2015).

[20] House of Commons debate, 1 Sep 2014 : Column 103. http://hansard.parliament.uk/Commons/2014-09-01/debates/14090125000001/MitochondrialReplacement(PublicSafety) (accessed July 6, 2017).

scientists can be reluctant to pursue legislative aims because of the risk of greater restriction. In this kind of climate, suggestions about a straightforward adoption of the UK model of liberal regulation to other jurisdictions should be made with extreme caution.

It is significant to note that the Mexico case exposed an extended time lag: when the birth of the 'first' was announced, no clinics had yet been licensed in the UK, despite the fact that the techniques by then were legal. Whereas some claimed that the UK process was excessively labored (and conversely, others considered it rushed), time will tell as to whether the UK position on MRT becomes an exemplar for others of how regulation can foster innovation.[21]

It is therefore important to note the particular context of UK biopolitics which facilitated MRT legalization—close yet permissive regulation; experience of conducting scientific and ethical reviews; an active and organized patient cohort; resources for supporting the review process, developing science and clinical care; and most importantly, the political will to support change. MRT research was extensively funded through the Wellcome Trust and Muscular Dystrophy UK, resources were available to carry out reviews and assess evidence, and the National Health Service has agreed to fund clinical services. Although commercial interests have not been key features of the discussions within the UK context, it is possible that fostering better international collaboration, and enhancing procedural transparency, could prove extremely valuable in guiding future progress. What is clear from these discussions is that legalization within the UK, the role of Mexico in the 'first' birth, the use of MRT in Ukraine for fertility issues[22] (which would be illegal in the UK), and the development of gene editing technologies (which has much wider applicability for both human health, embryo research and human enhancement) inform a new international landscape of MRT technologies and bring with it new global challenges.

[21] S.H. Harmon & D. Kale. *Regulating in Developing Countries: Multiple Roles for Medical Research and Products Regulation in Argentina and India*, 43 Tech. Soc. 10–22 (2015).

[22] A. Coghlan, *Exclusive: '3-parent' Baby Method Already used for Infertility*, New Scientist, Oct. 10, 2016. https://www.newscientist.com/article/2108549-exclusive-3-parent-baby-method-already-used-for-infertility/ (accessed Oct. 24, 2016).